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Fibrinolytic treatment of thrombus on prosthetic heart valves

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SUMMARY Fibrinolytic agents were administered for 13 episodes of thrombus formation on mitral or aortic valvar prostheses in 12 patients. The most common presenting features were pulmonary oedema (six cases) or arterial emboli (six cases). The diagnosis of thrombus formation was made by phonocardiography on the following criteria: (a) modifications of the prosthetic sounds (12 cases), (b) appearance of a valvar obstructive syndrome (10 cases).

The treatment consisted of streptokinase (100 000 units/h after a loading dose, seven cases) or urokinase using either low doses (75 000 to 112 500 units/h, three cases) or moderate doses (150 000 units/h, three cases) for one to four days.

Immediate complete regression of clinical and phonocardiographic anomalies was seen in eight cases. Incomplete improvement was seen in two patients, leading to operation: this was unsuccessful in one patient who had surgery on the third day, and was successful in the other on the 75th day. There were three failures leading to successful reoperative procedures in two patients and to an early death in the third patient suffering from acute myocardial infarction. One non-fatal haemopericardium was observed in a patient treated with streptokinase. No important side effect was noted during delivery in a pregnant woman.

During subsequent follow-up, a recurrent episode of thrombus formation was observed in one patient, treated by fibrinolytic therapy with success. One patient had an operation for a valve replacement six months after fibrinolytic treatment because of non-thrombotic valvar dysfunction; the outcome was fatal. Six patients are alive and in good condition, with a follow-up of six months to five years.

Thrombus formation represents the main late complication of valvar prostheses. Since the first published observation,[1] and the first successful treatment by new valve replacement,[2] many cases have been reported. Emergency surgical treatment, however, may be hazardous under some conditions, with a mortality rate about 50 per cent.[3] Taking into account the first reported successful treatment with streptokinase,[4] we decided to manage such patients initially with fibrinolytic therapy.

Subjects and methods

Twelve patients were treated for 13 episodes of thrombotic obstruction of a prosthetic valve. There were five men and seven women (including one who was 8 months pregnant), with ages ranging from 23 to 69 years (average 51 years).

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There were eight Starr-Edwards prostheses of the following types: four series 6120 in the mitral position (including one which was subject to a recurrent episode of thrombus formation in a patient with a chronic pulmonary artery thrombosis); one series 6400 in the mitral position; and three series 1260 in the aortic position. There were four Björk-Shiley prostheses, of which three were in the mitral position and one was in the aortic position.

The presenting features included pulmonary oedema in six cases (acute in three of them), systemic arterial emboli in six cases, angina pectoris in two cases (one of them having had a normal coronary arteriogram four months previously), myocardial ischaemia in one case, and myocardial infarction in two cases (one of them with low cardiac output (Table 1).

All patients received anticoagulant drugs. This

treatment produced an effect within the therapeutic range in eight episodes (seven patients), with prothrombin times, evaluated with rabbit brain thromboplastin, below 35 per cent. The treatment was inadequate in the other five patients (Table 2).

Table 1 *Clinical manifestations*

Symptoms	*No. of cases*
Acute pulmonary oedema	3
Subacute pulmonary oedema	3
Cerebral emboli	4
Angina pectoris	2
Limb emboli	2
Myocardial ischaemia	1
Myocardial infarction	2
Low cardiac output	1

CRITERIA FOR DIAGNOSIS

The diagnostic criteria were based on the association of abnormal prosthetic sounds and murmurs related to an obstructive syndrome.[5] Phonocardiograms were performed for all patients, using a Mingograf 81 seven-channel direct ink-writing recorder, providing a frequency response from 20 to 800 cycles. Chart speed was 100 mm per s. Carotid pulse was recorded with an EMT 5 105 transducer. Time intervals were corrected according to heart rate using the Bazett formula,[6] and carotid ejection time was calculated as a percentage of normal using the Hartman diagram.[7] Echocardiograms were performed on eight patients, using a Smith-Kline Ekoline 20-A apparatus. These two techniques were performed before, and 12, 24, and 48 hours after fibrinolytic therapy, taking care to use the same amplitude for all traces in the same patient.

The other investigations consisted of cinefluoroscopy (nine patients), left ventriculography (two patients), and left heart catheterisation (one case).

FIBRINOLYTIC TREATMENT

The fibrinolytic treatment used was streptokinase* in seven instances and urokinase in six instances. Urokinase† was chosen in case 3 because of previous allergic symptoms and in case 6 because of recent treatment by streptokinase. In the four other cases, it was an arbitrary choice.

Streptokinase was administered continuously via a peripheral vein with an infusion pump. According to recommendations,[8] an initial dose of 500 000 international units (IU) together with 50 mg hydrocortisone were administered over 30 minutes, followed by 100 000 IU per hour over a period of 12 to 96 hours. As soon as the fibrinogen level exceeded 1·5 g per l, heparin infusion was introduced to bring the patient's recalcification clotting time to at least twice the control value.[9]

Urokinase was administered empirically in the recommended doses, irrespective of body weight. Infusion was by a similar technique, using an

*Streptokinase (Hoechst Laboratories)
†Urokinase (Choay Laboratories)

Table 2

Case no.	*Sex*	*Age (y)*	*Weight (kg)*	*Prosthesis*	*Anticoag.*	*Symptoms*	*Diagnosis*	*Treatment*
1	M	47	62	M Björk	Adequate	Acute pulmonary oedema	PCG +, cine 0	SK 4 days
2	F	64	48	Ao Starr	Inadequate	Arterial emboli, myocardial infarction, shock	PCG +, cine 0	UK 1 day, 75 000 U/h
3	M	50	64	Ao Starr	Adequate	Angina pectoris	Coron, PCG +	UK 1 day, 112 500 U/h
4	M	54	70	Ao Starr	Inadequate	Cerebral embolism, myocardial infarction	PCG 0, cine 0, cineangio 0	SK 2 days
5	M	59	60	M Starr	Adequate	Subacute pulmonary oedema	PCG +, cine 0, echo 0	SK 1 day
6	Same patient				Adequate	Subacute pulmonary oedema	PCG +, echo 0	UK 2 days, 150 000 U/h
7	F	68	59	M Björk	Adequate	Acute pulmonary oedema	PCG +, cine ±, echo 0	SK 2 days
8	F	53	51	M Starr	Adequate	Subacute pulmonary oedema	PCG +, cathet +, cine +, echo 0	UK 2 days, 150 000 U/h
9	M	55	71	M Starr	Inadequate	Cerebral embolism, myocardial ischaemia	PCG +, echo +, cine +	UK 3 days, 300 000 U every 6 hours
10	F	57	56	M Björk	Adequate	Acute pulmonary oedema	PCG +, echo +, cine 0	UK 2 days, 150 000 U/h
11	F	26	52	M Starr	Inadequate (Pregnancy)	Arterial embolisms	PCG +, cine 0, echo 0	SK 12 hours
12	F	52	61	M Starr	Adequate	Cerebral embolism	PCG +, cine 0, cineangio 0	SK 2 days
13	F	23	52	Ao Björk	Inadequate	Cerebral embolism	PCG +, cine 0	SK 2 days

M, mitral; Ao, aortic; cine, cinefluoroscopy; echo, echocardiography; cineangio, cineangiography; PCG, phonocardiogram; Coron, coronary arteriography; Cathet, left catheterisation. +, Examination typical of thrombus. 0, No sign of thrombosis. ±, Equivocal examination.

initial dose of 150 000 IU over 30 minutes, followed by 75 000 to 150 000 IU per hour for 24 to 48 hours. Individual infusion rates were as follows: 75 000 IU per hour (1560 IU/kg) in case 2, 112 500 IU per hour (1760 IU/kg) in case 3, and 150 000 IU per hour in the three other patients (2500 IU/kg in case 6, 2940 IU/kg in case 8, 2680 IU/kg in case 10). Simultaneous heparin infusion was instituted to attain the modifications in the recalcification clotting time. In case 9 urokinase treatment consisted of 300 000 IU every six hours over three days using intermittent intravenous injections: this low dosage did not justify serum fibrinogen level measurements.

Heparin was replaced by oral anticoagulants after seven to 15 days of fibrinolytic therapy.

Results

Clinical details are summarised on Table 2. Diagnosis was made in all cases but one by phonocardiography.

MITRAL PROSTHESES (9 episodes)

(a) Before treatment

There was a positive diagnosis in nine episodes, relying on the following: a conspicuous decrease or disappearance of the opening click (all cases); associated with a prolonged diastolic rumble (cases 5, 6, 7, 8, 10, 11, 12); in cases 5, 6, 7, 8, 10, and 12 carotid ejection time was obviously reduced. In addition a late systolic murmur was noted twice in the patient with recurrent thrombosis (cases 5 and 6).

The traces showed a normal closing click in all patients and, when it could be measured, a normal second sound to prosthetic opening click interval (except for case 1, where it was shortened).

(b) After treatment

In six cases there was complete disappearance of the diastolic rumble as well as any systolic murmur, and recovery of a normal opening click. In case 12, the amplitude of the opening sound remained abnormal. For the last two patients (cases 9 and 10) the phonocardiogram remained unchanged.

AORTIC PROSTHESES (4 episodes)

(a) Before treatment

There was a positive diagnosis in all but one case (case 4) based on the occurrence of the following features compared with reference traces: a prolonged high frequency delayed peak systolic murmur in three patients (cases 2, 3, 13) with a palpable thrill in case 13; a decrease in the amplitude ratio of the aortic opening to the aortic closing sound (Hylen ratio) related to a conspicuously reduced opening click in cases 2 and 3 (in case 13 the association of a predominant decreased closing click led to an increase in this ratio, see Fig. 3); the development of a faint diastolic murmur in cases 2, 3, and 13; and finally the following carotid pulse modifications: increase of ejection time in two cases (3, 13), increase of half-rise time in all cases, and a coexistent slight "aortic stenosis-like" pattern with modification of the incisura in all cases.

(b) After treatment

The phonocardiogram remained completely unchanged in case 2. In the two other diagnosed cases (cases 3 and 13) the traces showed the complete disappearance of all the anomalies.

Other investigations included the following:

ECHOCARDIOGRAPHY (Table 2)

In two out of eight cases abnormal prosthetic motions were noted. In these two (cases 9 and 10) no improvement was seen.

CINEFLUOROSCOPY (Table 2)

Two out of 10 cases (cases 8 and 9) showed a clearly impeded ball excursion. In case 7, it was less obvious. In seven cases it was normal. After treatment, there was an improvement in only one of the two cases with definite abnormality (case 8).

TRANSSEPTAL LEFT HEART CATHETERISATION

This was performed in one case (case 8) and showed

mmediate results	*Follow-up*
uccess	Haemopericardium operated on 12th day; 6 month: surgery (prosthesis dysfunction), death
'ailure	Death 24th hour during transfer to surgical centre; necropsy: thrombosis
uccess	Well and alive after 5 years
'ailure	Surgery 20th day: thrombosis-Hancock
uccess	2nd thrombosis 75th day
uccess	Death after 2½ years (pneumonia). Necropsy: normal prosthesis
uccess	Well and alive after 3 years
uccess	Well and alive after 2 years
ailure	Surgery 8th day: thrombosis-Starr
'ransient clinical improvement	Surgery 3rd day: partial thrombosis lysis; operative death
uccess	Uterine haemorrhage, normal delivery, normal child; Alive and well after 2 years
linical and PCG improvement	Cerebral embolism at 8th day, surgery 75th day: thrombosis-Hancock
uccess	Alive and well after 6 months

a left atrioventricular gradient of 9 mmHg.

LEFT CINEANGIOCARDIOGRAPHY
This was performed twice (cases 4 and 12) without producing any positive evidence of thrombus.

EARLY SURGERY (five patients, Table 2)
OR A POSTMORTEM EXAMINATION (case 2)
These confirmed thrombus formation in all cases. There were organised thrombi on the rings and on the struts of Starr-Edwards prosthesis in cases 2, 4, 9, and 12 which impeded the motion of the balls. In case 2, an acute myocardial infarction was found with thrombus in the left coronary artery, presumably embolic in origin. In a fifth patient (case 10) a non-organised and non-occlusive thrombus was observed covering a small area of the disc of the Björk-Shiley prosthesis. The surgeon's impression was that the clot was friable, suggesting that partial lysis had occurred. Case 1 was operated upon six months after fibrinolytic treatment and the only surgical finding was dysfunction of the prosthesis. Case 6 died later from pneumonia. The prosthesis was normal.

FIBRINOLYTIC TREATMENT
In seven cases fibrinolytic treatment was with streptokinase and in six cases with urokinase.

Clinical course
The clinical course is set out in Table 2. For those treated with streptokinase, there were four immediate complete successes with a follow-up in the survivors of three years (case 7), two years (case 11), and six months (case 13). The fourth patient (case 1) was initially improved but developed progressive dyspnoea that led to late reoperation. Dysfunction of the prosthesis was found and the patient died after operation.

Of the three other cases treated with streptokinase, there was one initial success with complete clinical improvement, but thrombus formation recurred two and a half months later, leading to a second successful course of fibrinolytic treatment using urokinase (case 5); case 12 showed incomplete clinical and phonocardiographic improvement, leading to a successful reoperation on the 75th day; case 4 had a complete failure of fibrinolytic treatment but successful reoperation on the 20th day.

For those patients treated with urokinase there were three complete successes, with a follow-up of five years (case 3), two and a half years (case 5), and two years (case 8). In case 10 the clinical improvement was only transient, leading to reoperation on the third day, with surgical death.

For the last two cases there was complete failure of treatment: case 2, who suffered from myocardial infarction with cardiogenic shock, died 24 hours later before operation could be performed. Case 9 was successfully reoperated on a week after presentation. These two patients received very low doses of urokinase on a body weight basis (Table 2).

Fibrinogen levels
These are summarised in Table 3.

For streptokinase the maximal fibrinogen decrease (observed within 24 hours) ranged between 0 and 0·9 g/l in six cases. The fibrinogen level was 1·5 g/l in the seventh case.

For urokinase in the three patients receiving a 150 000 IU per hour dosage (1500 to 3000 IU/kg per hour) the fibrinogen decreased between 2 and 2·8 g/l. It remained unchanged in cases 2 and 3, who were receiving a smaller dose. It was not controlled in case 9 who was receiving intermittent small doses.

No significant correlation exists between this early clinical course, the fibrinogen decrease, and the duration of the treatment. We observed six successes among seven patients with a low fibrinogen level, one success among three patients with unchanged (or probably unchanged: case 9) levels, and two successes among three patients with intermediate levels (Table 3).

COMPLICATIONS
There were two patients with haemorrhage. Case 1 developed a haemopericardium after treatment with streptokinase for four days. A predisposing lesion was postoperative pericarditis, clinically diagnosed before administration of streptokinase on the following criteria: pericardial rub heard a week before thrombus formation and increase of cardiothoracic ratio after operation. Pericardio-

Table 3 *Fibrinogen levels*

Case no.	*Treatment*	*Fibrinogen (g/l)*		*Immediate results*
		Before treatment	*After treatment*	
1	SK	4·5	1·5	Success
2	UK	4·8	4·5	Failure
3	UK	6·2	5·9	Success
4	SK	2·7	0·8	Failure
5	SK	4·8	0·8	Success
6	UK	5·0	2·8	Success
7	SK	3·2	0·9	Success
8	UK	4·1	2·3	Success
9	UK	Not done	Not done	Failure
10	UK	3·9	2·0	Failure
11	SK	6·0	0	Success
12	SK	2·7	0·6	Success
13	SK	4·4	0·5	Success

SK, streptokinase; UK, urokinase.

centesis was successfully performed on the 12th day after treatment with streptokinase. Case 1 bled from the uterus during delivery and caesarean section was required.

Discussion

All types of prosthetic valves may develop thrombus, particularly the most commonly used: Starr-Edwards prostheses;[10 11] Björk-Shiley prostheses;[12 13] Lillehei-Kaster prostheses.[14]

This complication appears to be more frequent in the atrioventricular than in the aortic position. Its frequency is reduced by using effective anticoagulant treatment.[15] Nevertheless in eight out of 13 instances included in this paper thrombus formations occurred in spite of adequate treatment. The diagnosis may be suspected in any case with sudden reappearance of signs of valvar obstruction, especially pulmonary oedema, acute coronary insufficiency, and/or systemic arterial embolism.

In our experience, the most reliable positive contribution to the diagnosis of a thrombosed prosthesis is provided by the phonocardiogram. The alteration in the prosthetic clicks, especially the opening click, as first stressed for mitral prostheses by Spencer,[2] led to a positive diagnosis in 12 out of 13 instances of thrombus formation (92%). But the specific element of the obstructive type of dysfunction relies on the association with the prosthetic sound alterations of an obstructive phonocardiographic syndrome as previously described.[7] The main features of this syndrome are the appearance of a prolonged diastolic rumble for atrioventricular valves and of a delayed peak high frequency "stenotic like" systolic murmur with carotid pulse changes for the aortic prostheses. This phonocardiographic obstructive syndrome was present in 10 out of 13 patients (77%). In the mitral position, where thrombus formation is the usual cause of obstruction, prolonged diastolic rumble is always abnormal. Its significance is completely different from that of the brief functional rumble which may be heard on normal prostheses. Its diagnostic value is particularly important with the Björk prosthesis, often characterised by a faint or even absent opening click which does not *per se* indicate dysfunction.[7] This fact underlines the need for a careful recording technique to detect the abnormal rumble of malfunctioning prostheses, using an adequate gain, adequate frequencies (chiefly mid-frequencies), and sometimes manoeuvres to enhance the murmur (left lateral position, exercise, amyl nitrite). As for the second sound to opening click interval variation, it was unreliable in our study; the same applies to the closing sound and to regurgitant murmurs.

For aortic prostheses (especially of the Björk-Shiley type), the wide variation from patient to patient in the ratio of intensity of opening sound to closing sound calls for caution in the clinical interpretation of this as an isolated physical sign in the absence of previous phonocardiographic control. An apparent increase of this ratio may be present paradoxically even in the presence of valve dysfunction as a result of a predominant decrease in the closing click, as shown in our case 13 (Fig. 3). In the same way, slight isolated indentations on a carotid pulse tracing may exist with a normally functioning aortic Björk prosthesis and are not diagnostic of obstruction unless associated with timing abnormalities and systolic murmur modifications; it is essential to follow the latter since the systolic murmur observed with Björk prostheses may be somewhat longer and peak later than the one seen with Starr-Edwards prostheses. All these factors underline the diagnostic value of the association of several signs of obstruction, and also the need for systematic postoperative control tracings.

Despite similar phonocardiographic features, the thrombotic origin of the obstruction can be distinguished from aortic ball variance[16] by the effect of fibrinolytic therapy. The therapeutic improvement may be followed with serial phonocardiograms which may show regression of the auscultatory anomalies and modifications of the carotid ejection time (increases for thrombolysis in the mitral position and decreases for thrombolysis in the aortic position). We found that unchanged measurements implied persistent thrombus. Though very sensitive for the types of prostheses included in this paper, our phonocardiographic obstructive criteria may not be applicable to the more recent types of prostheses for which the normal phonocardiographic criteria (sounds as well as murmurs) differ from those of standard valves. This may limit the value of phonocardiographic detection of dysfunction.

Echocardiography provides an interesting contribution to the study of prosthetic valve function, but does not solve all the problems.[17] It may lead to a diagnosis of thrombosis when an abnormal prosthetic motion is displayed,[18] especially when compared with a previous recording.[19] Moreover, echocardiography may be usefully associated with phonocardiography for the identification of an opening sound which is delayed,[20] or inapparent, as for example with a Lillehei-Kaster prostheses,[14] For mitral prostheses with a short second sound to mitral valve opening interval, the study of the left ventricle and septal motion can help in distinguish-

ing between paravalvar regurgitation, left ventricular malfunction, and prosthetic obstruction.[14 21] In our patients, however, only two of eight recordings suggested thrombotic obstruction. Perhaps the introduction of cross-sectional echocardiography will lead to improved assessment.

It has been suggested that cinefluoroscopy may help when it shows alteration in the motion of a prosthetic valve. It was evident in only two of our patients, and doubtful in two other cases. Since the introduction of a radio-opaque marker in the recent Björk-Shiley prosthetic discs the correct identification of altered motion suggesting thrombotic obstruction may be easier.

Other investigations are invasive. Catheterisation may be useful. A right heart catheterisation may be performed easily using a Swan-Ganz catheter, but when an increase in the capillary wedge pressure exists it does not differentiate between left heart failure and prosthesis dysfunction. This does not apply to left heart catheterisation, which strongly suggests the diagnosis when a gradient is present, as in our case 8. Cineangiocardiography has also helped diagnosis in cases of aortic prostheses dysfunction.[12] These invasive procedures are difficult to perform however and make later fibrinolytic therapy hazardous.

Surgical cure of prosthetic thrombosis involves either simple thrombectomy, or more often the insertion of a new prosthesis. It does not prevent recurrent thrombosis as shown in Inberg's observation[22] and in our case 7. The risk is also considerable when operation is performed as an emergency procedure. In d'Allaines series,[3] it resulted in eight deaths (all but one emergency operations) out of 16 patients. This 50 per cent mortality rate is higher than that caused by reoperation for paravalvar leak (15 deaths out of 82 patients or 18%), which rarely requires an emergency procedure. The surgical risk of reoperation for thrombosis is lower when the haemodynamic condition is satisfactory.[13]

All these considerations justify the use of fibrinolytic therapy which may be used immediately without important risks even for patients in poor condition. Furthermore, surgery may still be performed if medical treatment fails, though few cases have been reported.[4 22–24] We have been using this treatment routinely since 1972, with satisfactory results. In our study of 13 cases we obtained eight immediate successes with complete disappearance of clinical and phonocardiographic anomalies. We also had two partial successes, one of these patients also surviving. But the possibility of recurrent thrombosis must be kept in mind: case 5 (later case 6) developed a second thrombus 75 days after the first course of treatment and was successfully treated with urokinase.

Our experience of six successful cases followed up from six months to five years shows that removal of the prostheses is not necessary after successful fibrinolytic therapy. It may sometimes be desirable to replace a thrombosed prosthesis with a biological valve, but even in such cases initial fibrinolytic therapy may permit better operating conditions and lower mortality.

Fibrinolytic therapy must be given only when a diagnosis of thrombus formation is clearly established by the non-invasive methods described above, and when its effect may be monitored by the same techniques over the first 24 hours. The absence of improvement must lead to reoperation, which may be performed two hours after fibrinolytic activity has been neutralised using protease inhibitors.

The choice of fibrinolytic drug, as well as the dosage, is still debated: either streptokinase or urokinase may be used in moderate (1500 to 3000 IU/kg per hour) or high (4400 IU/kg per hour)[25] doses. We prefer to use streptokinase because of its lower cost and its proven efficiency, but urokinase will be prescribed more often for allergic patients, or after previous treatment using streptokinase. Though our study does not lead to any definite therapeutic recommendations, it seems that most of the successes have been observed when the fibrinogen level was below or equal to 1·5 g/l (six out of seven patients). We had only one successful case among the three patients with high fibrinogen levels. This fact should favour the use of streptokinase or a high dose of urokinase.

The most serious complication was haemorrhage which occurred in two of our patients. In both cases, a predisposing factor was present: haemopericardium developed in a patient with clinically diagnosed postoperative pericarditis, and vaginal bleeding occurred during delivery in the other patient.

As for the return to anticoagulant treatment, we believe that heparin should usually be given as soon as the fibrinogen level reaches 1·5 g/l, generally within 24 to 48 hours of the beginning of fibrinolysis. Later on, if no operation has been done, oral anticoagulant therapy should be resumed. Non-invasive monitoring should be performed at close intervals, at least for the first year, for an early detection of recurrent thrombus formation.

Illustrative case histories

CASE 3

A 50-year-old man, weighing 64 kg, was operated

on in March 1973 for aortic valve stenosis. Preoperative coronary angiography gave normal findings. A Starr-Edwards prosthesis (1260) was inserted. Control of postoperative anticoagulant therapy (ethyldicoumarol) seemed satisfactory.

In July 1973, angina pectoris suddenly occurred and lasted until December 1973. At that time the patient was unable to hear the prosthetic sounds, and had no other symptoms. Thrombotic dysfunction of the prosthesis was diagnosed with the phonocardiogram on 17 December. The fibrinogen level was 6·2 g/l. Because of iodine allergy, another coronary arteriogram was not performed. Fibrinolytic therapy using urokinase was undertaken on the 18 December (112 500 IU/h, 1760 IU/kg per hour, over 24 hours). On 19 December, the patient again became aware of prosthetic sounds and the phonocardiogram returned to normal. The fibrinogen level was 5·9 g/l. Angina ceased and the patient has remained free of symptoms until now.

CASES 5 AND 6

A 59-year-old man weighing 60 kg underwent surgery in November 1974 for rheumatic mitral stenosis with atrial fibrillation, associated with a chronic right pulmonary artery thrombosis. A Starr-Edwards prosthesis of series 6120 was inserted. Subsequent anticoagulant treatment using acenocoumarol was apparently effective.

In October 1975, progressive subacute pulmonary oedema appeared with simultaneous decrease in prosthetic sounds. Cinefluoroscopy and an echocardiogram of the prosthesis remained normal, but the phonocardiogram indicated a diagnosis of thrombus involving the prosthesis. The fibrinogen level was 4·8 g/l.

On 5 November, thrombolytic therapy using streptokinase was undertaken over 24 hours. By 6 November, pulmonary oedema had regressed. The patient noted the reappearance of his prosthetic sounds, and the phonocardiogram became normal (Fig. 1). The fibrinogen level was 0·8 g/l. In spite of appropriate anticoagulant treatment, subacute pulmonary oedema recurred on 15 January 1976, and prosthetic sounds ceased. The phonocardiogram showed the same abnormal features as in November 1975, whereas the echocardiogram was again normal. The fibrinogen level was 5 g/l.

On 21 January, a second course of fibrinolytic treatment using urokinase (150 000 IU/h, 2500 IU/kg per hour, over 48 hours) was undertaken (Fig. 2). All the symptoms had disappeared by the 23 January. The fibrinogen level was 2·8 g/l. The phonocardiogram regressed to normal. The patient received the same anticoagulant therapy as previously and remained free of symptoms until August 1978. He then died because of a pulmonary infection and septicaemia. Necropsy ruled out any dysfunction of the prosthesis.

CASE 7

A 68-year-old woman weighing 59 kg underwent commissurotomy for mitral stenosis in 1957, followed by insertion of a Starr-Edwards mitral prosthesis (6120) in 1966. Apparently effective anticoagulant therapy was given using phenindione. The first occurrence of thrombus on the prosthesis necessitated operation on 30 December 1975 (insertion of a Björk-Shiley prosthesis). Subsequent anticoagulant therapy was in the therapeutic range.

On 14 February 1976, subacute pulmonary oedema occurred. Clinical examination disclosed a decrease in the amplitude of the prosthetic sounds. Echocardiogram was normal, whereas cinefluoroscopy gave equivocal results. Phonocardiogram led to the diagnosis of thrombosis. The prothrombin ratio was 27 per cent, and the fibrinogen level was 3·2 g/l.

On 15 February thrombolytic therapy using streptokinase was given for 48 hours. The fibrinogen level was 0·9 g/l after 12 hours and 1·7 g/l 48 hours later.

In spite of the patient becoming aware of valve sounds and regression of pulmonary oedema, the treatment had to be continued for a second 24 hour period until phonocardiographic anomalies disappeared completely. Valve function remains normal, with a follow-up of three years.

CASE 11

A 26-year-old woman, weighing 52 kg, underwent surgery in 1975 for mitral stenosis with insertion of a Starr-Edwards (6400) prosthesis. In 1976 she was pregnant, and in the eighth month of pregnancy anticoagulant therapy consisted of calcium heparinate. This treatment was ineffective. At the ninth month, two episodes of aphasia occurred and on 28 January 1977 the patient was admitted for an axillary embolism. Cinefluoroscopy and echocardiography were normal, but phonocardiography led to diagnosis of thrombotic involvement of the valve. The fibrinogen level was 6 g/l.

Treatment using streptokinase was undertaken. During the third hour, the signs of axillary embolism disappeared but a transient episode of aphasia occurred. Twelve hours after treatment was started a uterine haemorrhage occurred, with rupture of the membranes. The fibrinogen level was 0. Streptokinase was stopped and fibrinogen and protease inhibitors were prescribed. A

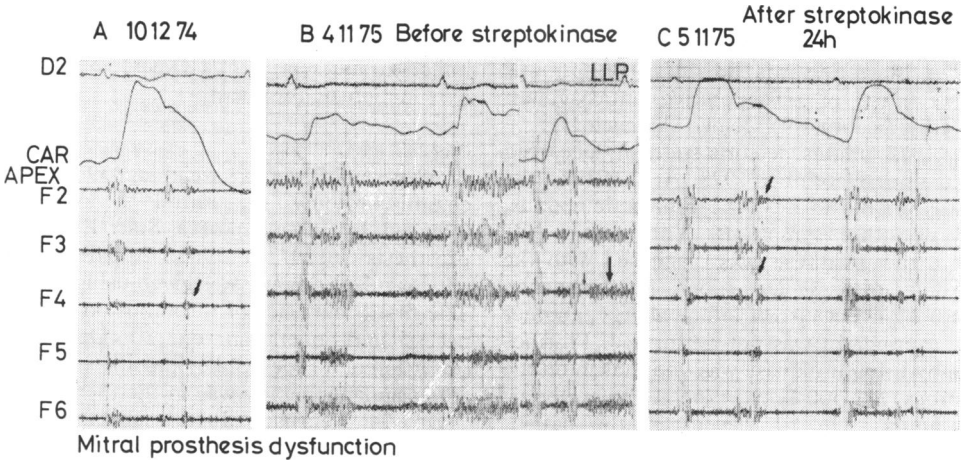

Fig. 1 *(case 5)—Starr-Edwards mitral prosthesis no. 6120. Obstructive dysfunction.* From top to bottom: *electrocardiogram, lead II; carotid pulse; apex phonocardiograms (F2 low frequencies, F3 middle frequencies, F4 middle high frequencies, F5 high frequencies, F6 audible frequencies). Chart speed 100 mm/s. LLP, left lateral position.* (A) *10/12/74: postoperative control phonocardiogram. Normal function as assessed by the closing and opening prosthetic click* (arrows): *amplitude is clearly greater than that of the second sound. Diastole free of vibrations. Ejection time 85 per cent of normal.* (B) *4/11/75: the disappearance of the opening click associated with the delayed* (little arrow) *prolonged diastolic rumble enhanced by left lateral position, led to the diagnosis of obstruction, reflected in the decrease in the carotid ejection time (70% normal). Also late systolic murmur and increased pulmonary component of second sound.* (C) *5/11/75: after 24 hours of streptokinase all the anomalies disappeared, the opening click* (oblique arrow) *reappeared, and carotid ejection time increased to 85 per cent of normal.*

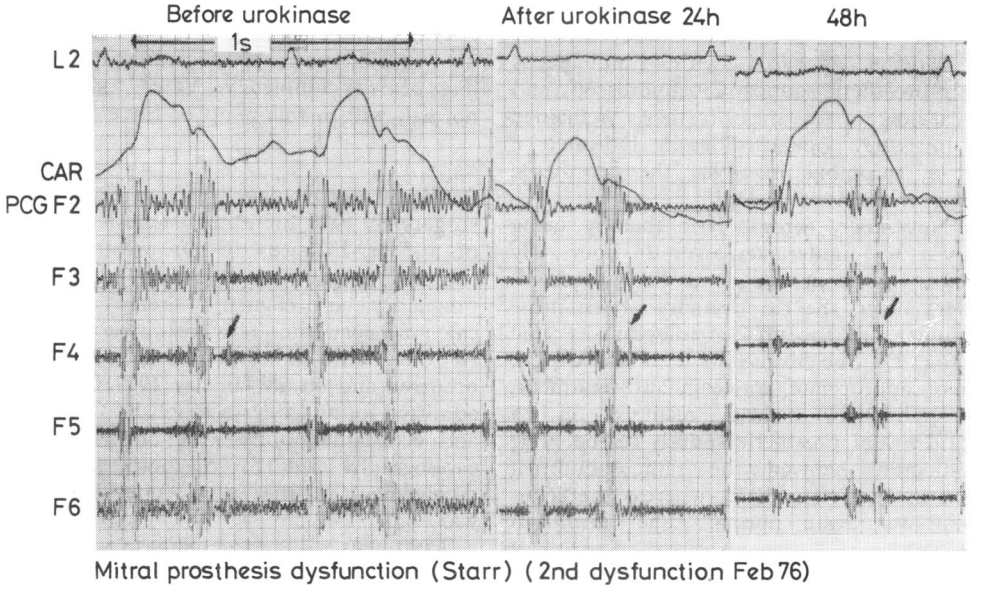

Fig. 2 *Same patient, recurrent dysfunction of the Starr-Edwards prosthesis. Same abbreviations as Fig. 1. Before urokinase the same conspicuous anomalies reappeared. After 24 hours of treatment, the improvement was considerable. Though there was incomplete persistence of systolic and diastolic vibrations, increase in pulmonary component of second sound, and carotid ejection time was still reduced (85% of normal). After 48 hours of urokinase, the phonocardiogram returned to normal with a normal opening click amplitude and a normal carotid ejection time (95% of normal).*

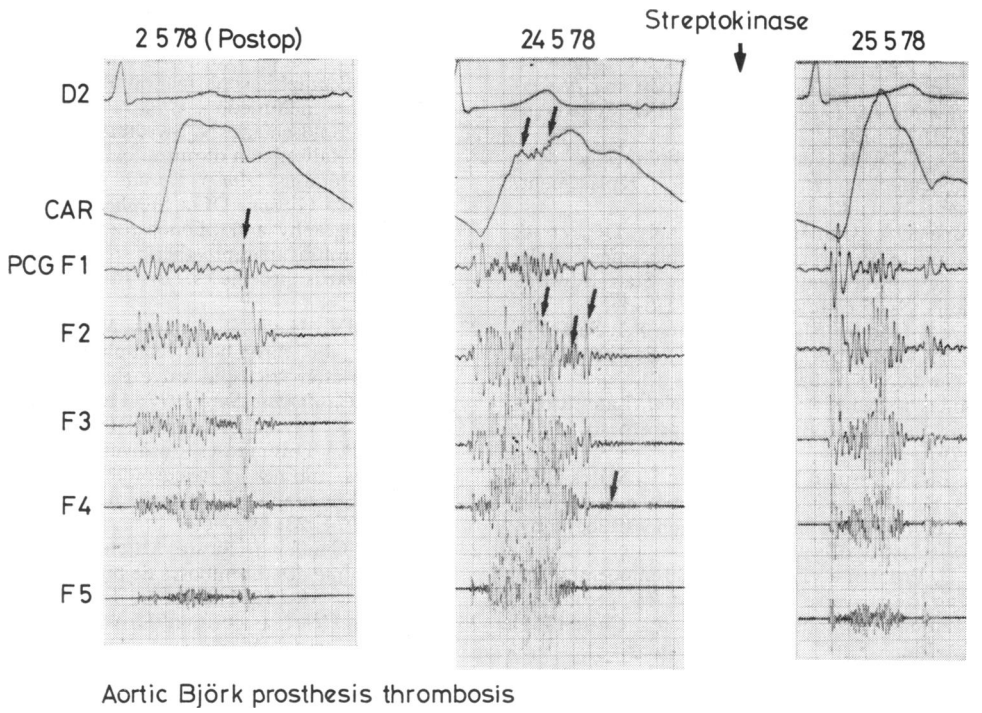

Fig. 3 *(case 13)—Aortic Björk prosthesis dysfunction. 2/5/78: postoperative control phonocardiogram. Normal function: a normal aortic Björk prosthesis phonocardiogram often involves a slightly prolonged systolic murmur, an AO/AC ratio clearly less than 1 (here 0·34), and some irregularities of the carotid pulse pattern. The systolic murmur is mainly displayed on the middle frequency, and rapidly decreases after its systolic peak. The ejection time (100%) and the half-rise time (0·047 s) are normal. Normal sequence of the second sound components. In diastole, there is discrete mitral opening snap resulting from previous mitral commissurotomy. 24/5/78—the diagnosis of dysfunction is assessed by the changes* (oblique arrows) *in the systolic murmur, in the amplitude of the click compared with that of the murmur (clearly less) and in the pattern and timing of the carotid pulse (ejection time: 125% of normal, half-rise time 0·074 s) leading to paradoxical splitting of the second sound. Note an unusual increase in the AO/AC ratio (0·46) caused by the simultaneous alteration of the two prosthetic clicks. There was also a faint diastolic murmur, and a systolic thrill. 25/5/78—after 24 hours of streptokinase there was improvement in the pattern of the carotid trace (ejection time 105% of normal, half-rise time 0·054 s) and phonocardiographic anomalies. Because of the clear increase of the closing click, the AC/AO ratio has paradoxically returned to 0·20 though dysfunction no longer existed.*

caesarean section was performed and the newborn child was normal. Heparin was started again 10 hours later. The phonocardiogram performed the following day was normal.

Subsequently, the patient again received acenocoumarol with a satisfactory follow-up of two years.

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